HALOTESTIN - fluoxymesterone tablet
Pharmacia and Upjohn Company

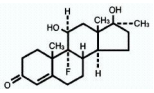
DESCRIPTION

HALOTESTIN Tablets contain fluoxymesterone, an androgenic hormone.

Fluoxymesterone is a white or nearly white, odorless, crystalline powder, melting at or about 240° C, with some decomposition. It is practically insoluble in water, sparingly soluble in alcohol, and slightly soluble in chloroform.

The chemical name for fluoxymesterone is androst-4-en-3-one, 9-fluoro-11,17-dihydroxy-17-methyl-, (11β,17β)-. The molecular formula is $C_{20}H_{29}FO_3$ and the molecular weight 336.45.

The structural formula is represented below:



Each HALOTESTIN tablet, for oral administration, contains 2 mg, 5 mg or 10 mg fluoxymesterone. Inactive ingredients: calcium stearate, corn starch, FD&C Yellow No. 5, lactose, sorbic acid, sucrose, tragacanth. In addition, the **2 mg** tablet contains FD&C Yellow No. 6 and the **5 mg** and **10 mg** contain FD&C Blue No. 2.

CLINICAL PHARMACOLOGY

Endogenous androgens are responsible for normal growth and development of the male sex organs and for maintenance of secondary sex characteristics. These effects include growth and maturation of the prostate, seminal vesicles, penis, and scrotum; development of male hair distribution, such as beard, pubic, chest, and axillary hair; laryngeal enlargement, vocal cord thickening, and alterations in body musculature and fat distribution. Drugs in this class also cause retention of nitrogen, sodium, potassium, and phosphorus, and decreased urinary excretion of calcium. Androgens have been reported to increase protein anabolism and decrease protein catabolism. Nitrogen balance is improved only when there is sufficient intake of calories and protein.

Androgens are responsible for the growth spurt of adolescence and for eventual termination of linear growth, brought about by fusion of the epiphyseal growth centers. In children, exogenous androgens accelerate linear growth rates, but may cause disproportionate advancement in bone maturation. Use over long periods may result in fusion of the epiphyseal growth centers and termination of the growth process. Androgens have been reported to stimulate production of red blood cells by enhancing production of erythropoietic stimulation factor.

During exogenous administration of androgens, endogenous testosterone release is inhibited through feedback inhibition of pituitary luteinizing hormone (LH). At large doses of exogenous androgens, spermatogenesis may also be suppressed through feedback inhibition of pituitary follicle stimulating hormone (FSH).

Inactivation of testosterone occurs primarily in the liver.

The half-life of fluoxymesterone after oral administration is approximately 9.2 hours.

INDICATIONS AND USAGE

In the male—HALOTESTIN Tablets are indicated for

1. Replacement therapy in conditions associated with symptoms of deficiency or absence of endogenous testosterone.
1. Primary hypogonadism (congenital or acquired) testicular failure due to cryptorchidism, bilateral torsion, orchitis , vanishing testis syndrome; or orchidectomy.
2. Hypogonadotropic hypogonadism (congenital or acquired)—idiopathic gonadotropin or LHRH deficiency, or pituitary-hypothalamic injury from tumors, trauma, or radiation.

2. Delayed puberty, provided it has been definitely established as such, and is not just a familial trait.

In the female—HALOTESTIN Tablets are indicated for palliation of androgen-responsive recurrent mammary cancer in women who are more than one year but less than five years postmenopausal, or who have been proven to have a hormone- dependent tumor as shown by previous beneficial response to castration.

CONTRAINDICATIONS

1. Known hypersensitivity to the drug

2. Males with carcinoma of the breast

3. Males with known or suspected carcinoma of the prostate gland

4. Women known or suspected to be pregnant

5. Patients with serious cardiac, hepatic or renal disease

WARNINGS

Hypercalcemia may occur in immobilized patients and in patients with breast cancer. If this occurs, the drug should be discontinued.

Prolonged use of high doses of androgens (principally the 17-α alkyl-androgens) has been associated with development of hepatic adenomas, hepatocellular carcinoma, and peliosis hepatis—all potentially life-threatening complications.

Cholestatic hepatitis and jaundice may occur with 17-α-alkyl-androgens. Should this occur, the drug should be discontinued. This is reversible with discontinuation of the drug.

Geriatric patients treated with androgens may be at an increased risk of developing prostatic hypertrophy and prostatic carcinoma although conclusive evidence to support this concept is lacking.

Edema, with or without congestive heart failure, may be a serious complication in patients with pre-existing cardiac, renal or hepatic disease.

Gynecomastia may develop and occasionally persists in patients being treated for hypogonadism.

Androgen therapy should be used cautiously in males with delayed puberty. Androgens can accelerate bone maturation without producing compensatory gain in linear growth. The effect on bone maturation should be monitored by assessing bone age of the wrist and hand every six months.

This drug has not been shown to be safe and effective for the enhancement of athletic performance. Because of the potential risk of serious adverse health effects, this drug should not be used for such purpose.

PRECAUTIONS

General

Women should be observed for signs of virilization which is usual following androgen use at high doses. Discontinuation of drug therapy at the time of evidence of mild virilism is necessary to prevent irreversible virilization. A decision may be made by the patient and the physician that some virilization will be tolerated during treatment for breast carcinoma.

Patients with benign prostatic hypertrophy may develop acute urethral obstruction. Priapism or excessive sexual stimulation may develop. Oligospermia may occur after prolonged administration or excessive dosage. If any of these effects appear, the androgen should be stopped and if restarted, a lower dosage should be utilized.

This product contains FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

Information for patients

Patients should be instructed to report any of the following: nausea, vomiting, changes in skin color, and ankle swelling. Males should be instructed to report too frequent or persistent erections of the penis and females any hoarseness, acne, changes in menstrual periods or increase in facial hair.

Laboratory tests

Women with disseminated breast carcinoma should have frequent determination of urine and serum calcium levels during the course of androgen therapy (See WARNINGS).

Because of the hepatotoxicity associated with the use of 17-alpha-alkylated androgens, liver function tests should be obtained periodically.

Periodic (every six months) X-ray examinations of bone age should be made during treatment of prepubertal males to determine the rate of bone maturation and the effects of androgen therapy on the epiphyseal centers.

Hemoglobin and hematocrit levels (to detect polycythemia) should be checked periodically in patients receiving long-term androgen administration.

Serum cholesterol may increase during androgen therapy.

Drug interactions

Androgens may increase sensitivity to oral anticoagulants. Dosage of the anticoagulant may require reduction in order to maintain satisfactory therapeutic hypoprothrombinemia.

Concurrent administration of oxyphenbutazone and androgens may result in elevated serum levels of oxyphenbutazone.

In diabetic patients, the metabolic effects of androgens may decrease blood glucose and, therefore, insulin requirements.

Drug/Laboratory test interferences

Androgens may decrease levels of thyroxine-binding globulin, resulting in decreased total T4 serum levels and increased resin uptake of T3 and T4. Free thyroid hormone levels remain unchanged, however, and there is no clinical evidence of thyroid dysfunction.

Carcinogenesis, mutagenesis, impairment Of Fertility

Animal data: Testosterone has been tested by subcutaneous injection and implantation in mice and rats. The implant induced cervical-uterine tumors in mice, which metastasized in some cases. There is suggestive evidence that injection of testosterone into some strains

of female mice increases their susceptibility to hepatoma. Testosterone is also known to increase the number of tumors and decrease the degree of differentiation of chemically-induced carcinomas of the liver in rats.
Human data: There are rare reports of hepatocellular carcinoma in patients receiving long-term therapy with androgens in high doses. Withdrawal of the drugs did not lead to regression of the tumors in all cases.
Geriatric patients treated with androgens may be at an increased risk of developing prostatic hypertrophy and prostatic carcinoma although conclusive evidence to support this concept is lacking.
This compound has not been tested for mutagenic potential. However, as noted above, carcinogenic effects have been attributed to treatment with androgenic hormones. The potential carcinogenic effects likely occur through a hormonal mechanism rather than by a direct chemical interaction mechanism.
Impairment of fertility was not tested directly in animal species. However, as noted below under Adverse Reactions, oligospermia in males and amenorrhea in females are potential adverse effects of treatment with HALOTESTIN Tablets. Therefore, impairment of fertility is a possible outcome of treatment with HALOTESTIN.

Pregnancy

Teratogenic effects
Pregnancy Category X. (See CONTRAINDICATIONS.)

Nursing mothers
HALOTESTIN is not recommended for use in nursing mothers.

Pediatric use
Androgen therapy should be used very cautiously in children and only by specialists aware of the adverse effects on bone maturation. Skeletal maturation must be monitored every six months by an X-ray of the hand and wrist (See WARNINGS).

ADVERSE REACTIONS

Endocrine and urogenital
Female: the most common side effects of androgen therapy are amenorrhea and other menstrual irregularities; inhibition of gonadotropin secretion; and virilization, including deepening of the voice and clitoral enlargement. The latter usually is not reversible after androgens are discontinued. When administered to a pregnant woman, androgens can cause virilization of external genitalia of the female fetus.
Male: Gynecomastia, and excessive frequency and duration of penile erections. Oligospermia may occur at high dosage.

Skin and appendages
Hirsutism, male pattern of baldness, seborrhea, and acne.

Fluid and electrolyte disturbances
Retention of sodium, chloride, water, potassium, calcium, and inorganic phosphates.

Gastrointestinal
Nausea, cholestatic jaundice, alterations in liver function tests, rarely hepatocellular neoplasms and peliosis hepatis (See WARNINGS).

Hematologic
Suppression of clotting factors II, V, VII, and X, bleeding in patients on concomitant anticoagulant therapy, and polycythemia.

Nervous system
Increased or decreased libido, headache, anxiety, depression, and generalized paresthesia.

Allergic
Hypersensitivity, including skin manifestations and anaphylactoid reactions.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class
Fluoxymesterone is a controlled substance under the Anabolic Steroids Control Act, and HALOTESTIN Tablets has been assigned to Schedule III.

OVERDOSAGE
There have been no reports of acute overdosage with the androgens.

DOSAGE AND ADMINISTRATION

The dosage will vary depending upon the individual, the condition being treated, and its severity. The total daily oral dose may be administered singly or in divided (three or four) doses.

Male hypogonadism

For complete replacement in the hypogonadal male, a daily dose of 5 to 20 mg will suffice in the majority of patients. It is usually preferable to begin treatment with full therapeutic doses which are later adjusted to individual requirements. Priapism is indicative of excessive dosage and is indication fortemporary withdrawal of the drug.

Delayed puberty

Dosage should be carefully titrated utilizing a low dose, appropriate skeletal monitoring, and by limiting the duration of therapy to four to six months.

Inoperable carcinoma of the breast in the female

The recommended total daily dose for palliative therapy in advanced inoperable carcinoma of the breast is 10 to 40 mg. Because of its short action, fluoxymesterone should be administered to patients in divided, rather than single, daily doses to ensure more stable blood levels. In general, it appears necessary to continue therapy for at least one month for a satisfactory subjective response, and for two to three months for an objective response.

HOW SUPPLIED

HALOTESTIN Tablets, round and scored, are available in the following strengths and colors:

2 mg (peach)
Bottles of 100 NDC 0009-0014-01

5 mg (light green)
Bottles of 100 NDC 0009-0019-06

10 mg (green)
Bottles of 30 NDC 0009-0036-03
Bottles of 100 NDC 0009-0036-04

Store at controlled room temperature 20° to 25°C (68° to 77°F) [see USP].

Rx only

Distributed by
Pharmacia & Upjohn Company
Division of Pfizer Inc, NY, NY 10017

810 804 708
692851
May 2002